REMARKS

Claim 12 has been cancelled. Claims 1, 7, 8, 15, 16, 17, 20, 26, 30, 33, 34, 35, 38, 44, 49, 52, and 53 have been amended. Claims 1, 7, 8, 12, 15-17, 19, 20, 26, 30, 33-35, 37, 38, 44, 49, 52, and 53 are pending in the instant application.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance.

I. The Rejection of Claims 1, 7, 8, 12, 15-17, 19, 20, 26, 30, 33-35, and 37 under 35 U.S.C. § 102

Claims 1, 7, 8, 12, 15-17, 19, 20, 26, 30, 33-35, and 37 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Hjort *et al.* (WO 00/50576). The Office Action stated:

> Hjort et al. teaches, e.g., at page 1, first paragraph, using a strain deficient in oxaloacetate hydrolase activity for production of polypeptides or metabolites. A polypeptide is a biopolymer. At page 34, second full paragraph, mutation of the oxaloacetate hydrolase gene nucleic acid sequence to produce the recited Aspergillus niger is taught. In the subsequent paragraph, mutation to eliminate expression of glucoamylase gene in the Aspergillus niger strain is taught. Also taught at this paragraph is the reduction or elimination of one or more of a number of enzyme activities: aminopeptidase, amylase, carbohydrase, carboxypeptidase, catalase, cellulase, chitinase, cutinase, cyclodextrin glycosyltransferase, deoxyribonuclease, esterase, alpha-galactosidase, beta-galactosidase, alpha-glucosidase, beta-glucosidase, invertase. laccase, lipase, mannosidase, mutanase, oxidase, a pectinolytic enzyme, peroxidase, phospholipase, phytase, polyphenoloxidase, proteolytic enzyme, ribonuclease, trans glutaminase, and xylanase. It is particularly taught that this sequence preferably encodes a proteolytic enzyme.

This rejection is respectfully traversed.

Under the standard required for anticipation under 35 U.S.C. § 102, the cited prior art reference is required to disclose every element of the claimed invention. *Lewmar Marine Inc. v. Barient Inc.*, 3 USPQ2d 1766 (Fed. Cir. 1987).

Hjort *et al.* disclose fungal host cells deficient in oxaloacetate hydrolase, which may be further deficient in one or more enzymes selected from the group consisting of aminopeptidase, amylase, carbohydrase, carboxypeptidase, catalase, cellulase, chitinase, cutinase, cyclodextrin glycosyltransferase, deoxyribonuclease, esterase, alpha-galactosidase, beta-galactosidase, glucoamylase, alpha-glucosidase, beta-glucosidase, invertase. laccase, lipase, mannosidase, mutanase, oxidase, a pectinolytic enzyme, peroxidase, phospholipase, phytase, polyphenoloxidase, proteolytic enzyme, ribonuclease, trans glutaminase, and xylanase.

However, Hjort *et al.* do not disclose a mutant of a parent *Aspergillus niger* strain comprising a modification of *glaA*, *asa*, *amyA*, *amyB*, *prtT*, and *oah*, as claimed herein.

For the foregoing reason, Applicants submit that the claims overcome this rejection under 35 U.S.C. § 102 and respectfully request reconsideration and withdrawal of the rejection.

II. The Rejection of Claims 38, 44, 49, 52, and 53 under 35 U.S.C. § 103

Claims 38, 44, 49, 52, and 53 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hjort *et al.* (WO 00/50576) in view of Fowler *et al.* (*Current Genetics* 18: 537-545, 1990). The Office Action stated:

> It would have been obvious to one of ordinary skill in the art to have practiced the method of creating the double mutant strain as taught by Hjort et al., with the mutation of the glaA gene being made particularly by the method taught by Fowler et al. The motivation to use the gene disruption method of Fowler et al. would have come from the teaching in Fowler et al. that complete removal of mRNA and protein activity could be accomplished thusly. This would have been an obvious manner to accomplish the teaching of Hjort et al. to eliminate glucoamylase expression, e.g., at the paragraph bridging pages 34 and 35.

This rejection is respectfully traversed.

An invention that is patentable in the United States must be, *inter alia*, non-obvious under 35 U.S.C. §103(a). An invention is not patentable if, although the invention is not identically disclosed or described in the prior art, the differences between the invention and the prior art are such that the invention as a whole would have been obvious at the time of the invention to a person having ordinary skill in the relevant art. 35 U.S.C. §103(a); *Graham v. John Deere Co.*, 383 U.S. 1, 13-14 (1966).

Most inventions arise from a combination of old elements, and each element may often be found in the prior art. *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998) (citing *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 698 (Fed. Cir. 1983)). The mere identification of each element in the prior art, however, is insufficient to defeat the patentability of the combined subject matter as a whole. *Id.* Rather, one must show a motivation to combine the references, *i.e.*, "reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *Id.* Even when obviousness is based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference. See *B.F. Goodrich Co. v. Aircraft Braking Sys. Corp.*, 72 F.3d 1577, 1582 (Fed. Cir. 1996).

A patent claim is obvious over a combination of prior art references only when "the prior

art would have suggested to one of ordinary skill in the art that [the claimed invention] should be carried out and would have a reasonable likelihood of success... . Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical,* 837 F.2d 469, 473 (Fed. Cir. 1988); *see also,* 35 U.S.C. §103. An invitation to experiment, alone, cannot make an invention obvious. *In re Dow,* 837 F.2d at 473.

Hjort *et al.* is discussed in Section V above. Fowler *et al.* discloses the regulation of the glucoamylase (*glaA*) gene of *Aspergillus niger.*

A valid case of *prima facie* obviousness requires that there must be a reasonable expectation of success found in the prior art. The "reasonable expectation of success" requirement has two distinct components. First, the guidance the reference provides must be sufficiently specific to direct the attention of one skilled in the art to the selection of parameters and choices necessary to obtain the invention. The prior art does not satisfy this requirement if it is necessary to vary all parameters, or to try each of numerous possible choices, in order possibly to arrive at a successful result. The second and related element of a reasonable expectation of success is that the prior art suggesting the desirability of the invention must enable one of ordinary skill in the art to produce it.

Applicants submit that both elements of a reasonable expectation of success are lacking in the cited references. First, the references, alone or in combination, provide no guidance to direct the attention of one skilled in the art to the selection of parameters and choices necessary to obtain the claimed invention. Second, the references, alone or in combination, do not enable one of ordinary skill in the art to produce the claimed invention.

While Fowler *et al.* dislcose methods for disrupting a glucoamylase gene (*glaA*) in an *Aspergillus niger* strain and Hjort *et al.* disclose a fungal host cell deficient in oxaloacetate hydrolase, which cell can be made further deficient in one or more enzymes selected from the group consisting of aminopeptidase, amylase, carbohydrase, carboxypeptidase, catalase, cellulase, chitinase, cutinase, cyclodextrin glycosyltransferase, deoxyribonuclease, esterase, alpha-galactosidase, beta-galactosidase, glucoamylase, alpha-glucosidase, beta-glucosidase, invertase. laccase, lipase, mannosidase, mutanase, oxidase, a pectinolytic enzyme, peroxidase, phospholipase, phytase, polyphenoloxidase, proteolytic enzyme, ribonuclease, trans glutaminase, and xylanase, Hjort *et al.* in view of Fowler *et al.* do not disclose a mutant of a parent *Aspergillus niger* strain comprising a modification of *glaA*, *asa*, *amyA*, *amyB*, *prtT*, and *oah*, as claimed herein. It is well known in the art that inactivation of multiple genes in a filamentous fungal strain can be deleterious to the viability of the strain. Consequently, one skilled in the art based on Hjort *et al.* in view of Fowler *et al.* would not have a reasonable

expectation of success that a viable mutant of a parent *Aspergillus niger* strain could be constructed comprising a modification of *glaA*, *asa*, *amyA*, *amyB*, *prtT*, and *oah* for the expression of a heterologous polypeptide. The knowledge in the cited references may make it "obvious to try" to construct a mutant of a parent *Aspergillus niger* strain comprising a modification of *glaA*, *asa*, *amyA*, *amyB*, *prtT*, and *oah* for use as a host cell for producing heterologous proteins, but the "obvious to try" standard is inadequate to render the claimed invention obvious without some teaching in the prior art which gives a reasonable expectation of success in achieving that goal. At most, Hjort *et al.* in view of Fowler *et al.* is merely an invitation to experiment An invitation to experiment, alone, cannot make an invention obvious. *Id.*

Applicants assert, therefore, that it would not have been *prima facie* obvious at the time of Applicants' invention to construct a mutant of a parent *Aspergillus niger* strain comprising a modification of *glaA*, *asa*, *amyA*, *amyB*, *prtT*, and *oah* for use as a host cell for producing heterologous proteins.

Applicants submit, therefore, that the claims overcome this rejection under 35 U.S.C. § 103(a) and respectfully request reconsideration and withdrawal of the rejection.

III. The Rejection of Claims 1, 7, 8, 12, 15-17, 19, 20, 26, 30, 33-35, 37, 38, 44, 49, 52, and 53 under 35 U.S.C. § 112, First Paragraph

Claims 1, 7, 8, 12, 15-17, 19, 20, 26, 30, 33-35, 37, 38, 44, 49, 52, and 53 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. The Office Action stated:

> Were the skilled practitioner to have attempted to practice the invention where the gene in question could "encode" a molecule other than a nucleic acid or a polypeptide, said practitioner first would have turned to the specification for guidance. However, no mention of how to transfer information beyond the encoded enzyme was made. Next, said practitioner would have turned to the prior art for such guidance, but again, the art offered no such teachings. Finally, the skilled practitioner would have been forced to turn to empirical experimentation to accomplish this. However, such would involve a fundamental change to the scheme by which genetic information is encoded, passed along and utilized. A means of copying sequence information form the enzyme (polypeptide) would be required in the cell, and such would clearly be an enormous experimental undertaking, representing undue experimentation.

Applicants have amended the claims to recite in part "heterologous polypeptide" in place of "heterologous biological substance".

Applicants submit, therefore, that the specification complies with the enablement

requirement and respectfully requests reconsideration and withdrawal of the rejection.

V. The Rejection of Claims 15, 33, and 52 under 35 U.S.C. § 112, Second Paragraph

Claims 15, 33, and 52 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite on the ground that the claims recite "the mutant strain produces at least 25% less glucoamylase and one or more enzymes selected from...", but it is not clear if the "one or more enzymes" are produced at least 25% less, or only glucoamylase.

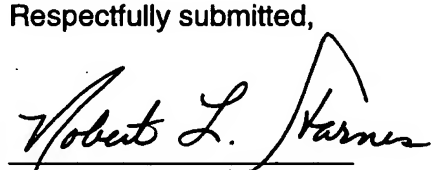
Claims 15, 33, and 52 have been amended to recite in part "the mutant strain produces at least 25% less enzyme for each of glucoamylase, acid stable alpha-amylase, neutral alpha-amylase A, neutral alpha-amylase B, protease, and oxalic acid hydrolase compared to the parent *Aspergillus niger* strain when cultured under identical conditions".

For the foregoing reason, Applicants submit that the claims overcome the rejections under 35 U.S.C. § 112 and respectfully request reconsideration and withdrawal of the rejections.

VI. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,



Date: January 25, 2007

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